REMARKS

The Amendments

The amendment to claim 25 recites the essential absence of polyvinylpyrrolidone in the compositions. Support for this amendment is found in the specification at page 8, lines 16-17, of the specification, and in several original claims. Claim 37 is amended to eliminate extraneous language and address the 35 U.S.C. §112 rejection. These amendments do not limit the scope of the claims. Claim 42 is amended to address the 35 U.S.C. §112 rejection, as discussed below. Support for the new "drying" recitation is found, for example, in the specification at page 16, lines 12-17, and in the Examples. Support for new dependent claim 68 is found in the specification, for example, at page 18, lines 13-14.

It is submitted that the above amendments would put the application in condition for allowance or materially reduce or simplify the issues for appeal. The amendments essentially incorporate previously claimed and/or argued limitations into the independent claims (i.e., the essential absence of polyvinylpyrrolidone into claim 25), or remove or clarify extraneous terms (i.e., in claims 37 and 42). Thus, they do not raise new issues or present new matter. Also, the amendments do not present additional claims without the cancellation of an at least even number of finally rejected claims. The amendments have been made to expedite prosecution by limiting the claims to preferred embodiments which even more clearly distinguish the cited prior art and address the 35 U.S.C. §112 rejections, thus, simplifying the issues for possible appeal. The amendments were not earlier presented because it is not believed such limitations were necessary but they are made to expedite prosecution of these narrower embodiments. Accordingly, it is submitted that the requested amendments should be entered.

To the extent that the amendments avoid the prior art or for other reasons related to patentability, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art or otherwise unpatentable to applicants. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejections under 35 U.S.C. §112

The two rejections under 35 U.S.C. §112, second paragraph, are rendered moot by the removal of the terms from the claims which gave rise to the rejections.

To clarify the record as to the "granulating" of the estrogen-cyclodextrin complex, applicants reiterate that the conditions under which granulation occurs are not of "critical importance in the practice of the instantly claimed method," as alleged in the Office Action. The disclosure does not support the allegation in the Office Action that particular granulation conditions are necessary to achieve the claimed invention. In the broadest description of the invention, the description only discusses granulation in general. Specific ways of carrying out the granulation to avoid certain aspects found to be detrimental to stability are discussed but as separate alternative embodiments, not as requirements. Specifically, claim 42 is directed to a preferred embodiment wherein granulation is conducted together with drying (as now clarified in the instant claim) to limit exposure of the estrogen-cyclodextrin complex to water. See, e.g., page 6, lines 17-29; and, page 16, lines 12-17. However, the disclosure provides other embodiments which relate to exclusion of polyvinylpyrrolidone or other oxidizing substances; see, e.g., page 7, line 28, to page 8, line 17.

There is no basis to support the allegation that the invention cannot be achieved without reciting some specific granulation conditions in the claims. Alternatively, if the exclusion of certain components, namely water (by drying) and polyvinylpyrrolidone from the excipients, is considered a "granulating condition" then the claims now specifically recited at least one of those conditions. One of ordinary skill in the art, based on their knowledge of the art and reading of applicants' specification, would clearly understand the metes and bounds of the current claims and be able to practice the invention without undue experimentation. That means/conditions for granulating were known in the art is demonstrated, for example, by the Backensfeld reference cited in the prior art rejections. The claimed inventions utilize known granulating techniques but add drying steps or exclude polyvinylpyrrolidone. The above amendments are believed to make this clear, although this was believed to have been clearly described in the specification already.

Thus, the rejection under 35 U.S.C. §112 should be withdrawn.

The Rejections under 35 U.S.C. §103

The rejections of claims 25 and 28-31 and of claims 47-62 under 35 U.S.C. §103, as being obvious over Backensfeld (U.S. Patent No. 5,798,338) in combination with Parikh (U.S. Patent No. 6,228,399), Pitha (U.S. Patent No. 4,596,795) and Krattenmacher (*Contraception* article) or obvious over these references further in view of Simmons (U.S. Patent No. 4,154,820) are respectfully traversed.

Applicants' invention is directed to an improvement over the Backensfeld invention. Applicants have discovered means by which more storage stable estrogen-cyclodextrin complexes can be provided. Obviously, providing such a pharmaceutical with enhanced storage stability provides a significant advantage and is an advance in the art deserving of patent protection. Particularly, applicants have discovered that the stability of the complex is improved if the complex is provided as a granulate preparation wherein the use of polyvinylpyrrolidone (PVP) as an excipients in the granulation is avoided and, thus, the product is essentially free of PVP. See, e.g., page 7, line 28, to page 8, line 17, of the specification, and the comparative example discussed below. Applicants have further discovered that the stability of the complex is improved if the complex is prepared by granulating which also involves drying steps to limit the exposure of the complex to water. See, e.g., page 6, lines 17-29; and, page 16, lines 12-17, of the specification.

Neither Backensfeld nor any of the other cited references, alone or together, disclose or suggest the advantages of applicants' inventions or the means of achieving such advantages, as recited in the instant claims.

The rejected claims all depend on claim 25 which recites a composition containing a granulated preparation of an estrogen-cyclodextrin complex, which composition is essentially free of PVP. The composition exhibits the advantageous storage stability properties.

In the Office Action, reference was made to Example 3 of Backensfeld as showing an embodiment wherein the PVP content was well below 2% by weight. This is a misinterpretation of Backensfeld. A correct reading of Example 3 would make clear that the total weight of the tablet is 55 mg, not 55,000 mg. The text of example (see col. 3, line 38) clearly states that the tablet has a weight of 55 mg. The recitation in the table of 55,000 mg (col. 3, line 50) is an obvious typographical error. In European usage, decimal points are often indicated by commas. This was obviously carried over into this patent which initially derived from a European application. Addition of the individual components also makes

clear that the total weight is 55 mg. Accordingly, the weight percent of PVP in the Backensfeld composition is 4.9%. This distinction of Backensfeld from the instant claims is even more glaring in view of the claims now reciting that they are essentially free of PVP. Thus, the only instance in which Backensfeld prepares a granulate of its composition requires the use of a significant amount of PVP. There is no teaching or suggestion of a granulate composition free of PVP. Accordingly, Backensfeld fails to establish a prima facie case of obviousness against instant claim 25, or claims dependent thereon.

The secondary references provide no teachings which would suggest modifying Backensfeld to remove or limit the PVP in its granulate compositions. Thus, the combination of Backensfeld with these references also fails to establish a prima facie case of obviousness.

For these reasons alone, the rejections under 35 U.S.C. §103 should be withdrawn.

Although it is unnecessary, because there is no prima facie case of obviousness, applicants' specification provides comparative data which further supports the nonobviousness of the claims. As discussed in applicants' previous reply, the specification provides a comparative showing that compositions comprising a granulated preparation of a complex according to Example 3 of Backensfeld have poor stability with respect to the concentration of ethinylestradiol in comparison to a granulated preparation according to the instant claims. Example 1 of the present patent application prepares and tests for stability a composition according to Example 3 of Backensfeld. The tests show that, following storage at 40°C for 12 months, only 76% of the initial content of ethinylestradiol is present in the granulated composition. See the data for tablet A in table 1.3 of the specification. Thus, it has been shown that the only specifically described granulate composition of Backensfeld does not meet the claim recitation regarding estrogen stability, i.e., "estrogen is in an amount of at least 90% w/w in relation to the initial content of said estrogen after storage for 12 months at 40°C and 75% relative humidity (RH)." In contrast, the stability of a composition according to the present invention in a side-by-side test is shown to be stable. Nearly 100% of the initial content of ethinylestradiol is maintained in a composition of the present invention following storage at identical test conditions, see data for tablet E in table 1.3 of Example 1.

The Office Action discounts the comparison on several bases.

First, it is alleged that a side-by-side comparison is not being provided because the comparative composition contains PVP and applicants' composition does not. But this is

exactly what is being compared. Example 1, tablet A, of the comparison duplicates the Backensfeld example which requires PVP. The example according to the invention is absent PVP, in accordance with claim 25.

Second, the "start" amounts shown in Table 1.3 are questioned. However, in view of the specification text on page 24, lines 5-8, and the knowledge of one of ordinary skill in the art, it would be immediately recognized that the data relate to the recovery of the estrogen (EE) in respect of the content of EE that was added to each formulation before the manufacturing steps. The "start" amount would obviously be the amount of EE at the time point of starting the stability study, which is just after finalizing the manufacturing of the product. Thus, in tablet A, some of the EE is already lost at the start point due to degradation during the manufacturing step (presumably this is because Backensfeld includes no drying step during granulating). This is why there is only 93.1% w/w of the initial amount of EE remaining in the tablet. Further significant degradation of the tablet A occurs over time.

In addition to the above, further variation from a 100% starting point is a reflection of a range of error, conventional in the art. The data reflects the actual amount of EE as determined in the product at the specified time points divided by the nominal amount of EE and then multiplied by 100. This kind of assessment is normally applied in the pharmaceutical industry. Due to variations in the production as well as the chemical analyses, the resulting amount of EE will not read 100%, but read an amount close thereto including an amount higher than 100%. Therefore, amounts of EE in the range of 97-103% indicate that the amount of EE applies to the nominal 100% of EE present at the time of initiating manufacturing of the composition.

If necessary, applicants can provide a declaration to describe these details of the data. But it is believed that these would have been evident to one of ordinary skill in the art. Further, they are not believed necessary in the absence of a prima facie case of obviousness over the cited art.

For all of the above reasons, it is urged that the rejections under 35 U.S.C. §103 should be withdrawn.

Method Claims

The method claims 37 and 42 and claims dependent thereon were not rejected over the prior art. Because it is believed the 35 U.S.C. §112 rejections are overcome, these

method claims would appear to be allowable.

However, certain statements in the Office Action would appear to impact on these claims and, thus, the following comments are provided.

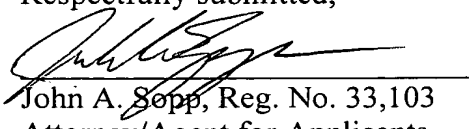
It is pointed out in the Office Action that Backensfeld teaches drying of its composition in Example 1 (col. 3, lines 10-11). However, Example 1 does not include a granulating step and does not prepare a composition having a granulate preparation of the estrogen-cyclodextrin complex. Thus, Backensfeld fails to teach or suggest any preparation of estrogen-cyclodextrin complex which involves both granulation and drying to provide a granulate having low humidity, such as recited in instant claim 42. When Backensfeld does granulate its product (see Example 3), no drying step is disclosed and the granulation is conducted using an aqueous solution. Thus, there is no suggestion of applicants' method or of a product with a low humidity level. Accordingly, Backensfeld fails to provide any prima facie case for obviousness of applicants' method claim 42. The secondary cited references teach nothing regarding granulating or drying and, thus, do not cure the deficiencies of Backensfeld.

Claim 37 is additionally distinguished because, as discussed above, the cited prior art fails to teach or suggest a granulate preparation essentially free of PVP.

The Office Action attempts to shift the burden of proof back to applicants to show nonobviousness (see the middle of page 6 of the Office Action). Although this may be appropriate in certain circumstances, it is not appropriate here. The PTO has the burden to at least provide a prima facie case of obviousness. There is no suggestion at all of the claimed method in the cited prior art. Thus, the PTO has not met its burden of proof and the burden cannot be shifted to applicants. Thus, the prior art does not support a rejection of claim 37 or claim 42 and claims dependent thereon.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

Respectfully submitted,



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